

measurements of changes in said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising: (a) comparing said measured biological response profile to a library of artifact signatures to generate an artifact template, each of said artifact signatures comprising measurements of amplitudes of said changes in said cellular constituents corresponding to different levels of said one or more experimental variables, said artifact template comprising an artifact signature having greatest similarity to said biological response profile, said comparing comprising pattern matching of said measured biological response profile against said library; and (b) subtracting said artifact template from said measured biological response profile, thereby removing said one or more artifacts from said measured biological response profile.

#### REMARKS

Claims 58-64 and 70-76 were pending in the present application. Claims 58-59 and 71-72 have been amended to clarify the present invention. Upon entry of the above-made amendments, claims 58-64 and 70-76 will be pending in the present application. A marked version showing changes made to the amended claims is attached hereto as Exhibit A. A clean version of the pending claims, as amended, is attached hereto as Exhibit B.

Claims 58 and 71-72 have been amended to clarify that in the claimed methods, each of the artifact patterns comprises *measurements of changes* in the cellular constituents resulting from deviation of one or more experimental variables from desired values (emphasis added). Claims 59 and 71-72 have been amended to clarify that in the claimed methods, each of the artifact patterns or artifact signatures comprises *measurements of amplitudes of the changes* in the cellular constituents resulting from deviation of one or more experimental variables from desired values (emphasis added). Support for the amendments is found in the specification at, e.g., page 34, line 23 through page 35, line 9.

No new matter has been added by these amendments. Entry of the foregoing amendments and the following remarks are respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 103(a)  
SHOULD BE WITHDRAWN

Claims 58-61 and 71-73 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 6,232,066 ("Felder") alone, or, alternatively, over Felder in view of U.S. Patent No. 5,866,331 ("Singer"). In particular, with respect to Felder, the Examiner contends that Felder discloses the use of control probes and that Felder motivates the removal of artifacts or undesired signals by comparison to such control probes, thereby making the instantly claimed invention unpatentable. The Examiner also contends that one such undesired signal is the background signal. With respect to Felder in view of Singer, the Examiner contends that Singer also discloses background subtraction in fluorescence signal processing, e.g., background or dark current subtraction. Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Felder teaches compositions, apparatus and methods for concurrently performing multiple biological or chemical assays. In Felder, positive control probes are used as internal standards for normalization purposes. Examples of such positive control probes include probes specific to house-keeping genes which are not expected to be modulated by, e.g., the agents being tested. Felder also teaches the use of negative control probes which are known not to interact with the target. Felder also teaches the use of probes specific to genes that are known to be induced as part of certain biological process, e.g., apoptosis, for determination of side effects of an agent. In Felder, background subtraction is also used.

Applicants respectfully point out that the presently claimed invention is directed to methods of removing artifacts from measured biological response profiles comprising measurements of a plurality of cellular constituents of a living cell or organism in response to a perturbation to said living cell or organism. The artifact patterns or artifact signatures that

are removed by the presently claimed method comprise *measurements of changes or measurements of amplitudes of changes in said cellular constituents resulting from deviation of one or more experimental variables from desired values* (emphasis added). Thus, an artifact of the present invention comprises changes due to deviation of one or more experimental variables from desired values in measurements of the same cellular constituents for which measurements are comprised in the biological response profiles. That is, the biological response profile comprises measurements of cellular constituents, and the artifact pattern comprises measurements of changes in these same cellular constituents. This is contrary to Felder in which some "other" cellular constituents, e.g., house-keeping genes or genes relating to some side effects, are measured and used. By teaching the use of control probes specific to such other cellular constituents, Felder teaches or suggests nothing about artifacts which comprise measurements of changes in the same cellular constituents for which measurements are comprised in the biological response profiles. As such, Felder teaches or suggests nothing about a method of removing such artifacts from measured biological response profiles.

With respect to background subtraction, Applicants respectfully point out that, as discussed above, an artifact in the presently claimed invention comprises measurements of *changes in cellular constituents resulting from deviation of one or more experimental variables from desired values*, i.e., changes in cellular constituents themselves. On the other hand, background signals are not measurements of changes in cellular constituents resulting from deviation of one or more experimental variables from desired values, but, rather, are measures of inaccuracies in signal measurements, which are independent of changes in cellular constituents. As an example, Applicants respectfully point out that, although levels of gene transcripts may be changed due to deviation of one or more experimental variables from desired values, thereby leading to artifacts in measured biological profiles, background signals arising during the determination of such changes in levels of gene transcripts are not themselves changes in levels of gene transcripts due to deviation of these experimental variables from desired values, and, therefore, are not the artifacts that are removed by the methods of the presently claimed invention. To make the claim language more clearly describe the invention, Applicants have amended claims 58-59 and 71-72 to clarify that an artifact pattern (or signature) comprises *measurements of changes (or measurements of*

*amplitudes of changes) in said cellular constituents resulting from deviation of one or more experimental variables from desired values* (emphasis added). Therefore, Felder does not render the presently claimed invention obvious. Applicants respectfully submit that the rejection of claims 58-61 and 71-73 under 35 U.S.C. § 103(a) based on Felder should be withdrawn.

Singer teaches a method for determining the total fluorescence intensity of a single fluorochrome. In Singer, background subtraction and dark current subtraction are used. Singer does not teach or suggest what is missing in Felder, i.e., artifacts comprising measurements of *changes in cellular constituents resulting from deviation of one or more experimental variables from desired values*. Nor does Singer teach or suggest a method of removing such artifacts from measured biological response profiles. Therefore, Felder in view of Singer does not render the presently claimed invention obvious. Applicants respectfully submit that the rejection of claims 58-61 and 71-73 under 35 U.S.C. § 103(a) based on Felder in view of Singer should be withdrawn.

#### THE OBJECTION TO CLAIMS SHOULD BE WITHDRAWN

Claims 62-64, 70 and 74-76 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. As discussed above, the base claims 58 and 71-72, as amended, upon which claims 62-64, 70 and 74-76 depend, are not rendered obvious by Felder or Felder in view of Singer. The objection to claims 62-64, 70 and 74-76 should therefore be withdrawn.

#### CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection or objection has been successfully overcome or obviated, and that all the pending claims are

in condition for allowance. Withdrawal of the Examiner's rejection and objection, and allowance of the application, are respectfully requested.

Respectfully submitted,

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Enclosures

**EXHIBIT A: MARKED VERSION OF THE AMENDED CLAIMS**

U.S. APPLICATION SERIAL NO. 09/220,275

(ATTORNEY DOCKET NO. 9301-039-999)

(as amended October 18, 2002)

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58. (Four Times Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising measurements of a plurality of cellular constituents of a living cell or organism in response to a perturbation to said living cell or organism, each of said one or more artifacts comprising an artifact pattern comprising measurements of changes in [measurements of] said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising subtracting said one or more artifact patterns from the measured biological response profile, thereby removing said one or more artifacts from said measured biological response profile.

59. (Three Times Amended) The method of claim 58, wherein each of the one or more artifact patterns comprises measurements of amplitudes of said changes in [amplitudes of said measurements of] said cellular constituents associated with the artifact to which the artifact pattern corresponds.

71. (Three Times Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising measurements of a plurality of cellular constituents of a living cell or organism in response to a perturbation to said living cell or organism, each of said one or more artifacts comprising measurements of changes in [measurements of] said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising subtracting an artifact template from the measured biological response profile, wherein said artifact template comprises an artifact signature having greatest similarity to said biological response profile and is obtained by a method comprising comparing said measured biological response profile to a library of artifact signatures, each of said artifact signatures comprising measurements of amplitudes of said changes in [amplitudes of measurements of] said cellular constituents corresponding to different levels of said one or more experimental variables, said

comparing comprising pattern matching of said measured biological response profile against said library; thereby removing said one or more artifacts from said measured biological response profile.

72. (Twice Amended) A method for removing one or more artifacts from a measured biological response profile, said measured biological response profile comprising measurements of a plurality of cellular constituents of a living cell or organism in response to a perturbation to said living cell or organism, each of said one or more artifacts comprising measurements of changes in [measurements of] said cellular constituents resulting from deviation of one or more experimental variables from desired values, said method comprising: (a) comparing said measured biological response profile to a library of artifact signatures to generate an artifact template, each of said artifact signatures comprising measurements of amplitudes of said changes in [amplitudes of measurements of] said cellular constituents corresponding to different levels of said one or more experimental variables, said artifact template comprising an artifact signature having greatest similarity to said biological response profile, said comparing comprising pattern matching of said measured biological response profile against said library; and (b) subtracting said artifact template from said measured biological response profile, thereby removing said one or more artifacts from said measured biological response profile.